CLAIM LISTING

Claims 1, 4-6, 11 and 13 have been amended. Claims 2-3 and 10 have been canceled. Claims 1, 4-6, 11, 13 and 14 are now pending. This listing of claims will replace all prior versions and listings of claims in the Application.

Listing of Claims:

WHAT IS CLAIMED IS:

Claim 1 (currently amended): A method for determining whether a human subject is at risk for developing obesity comprising ~~the steps of~~:

~~obtaining~~ assaying a sample from a human subject, said sample comprising a TBC1D1-encoding nucleic acid molecule or a complement thereof, ~~and~~ to determine if there is ~~detecting~~ an alteration in said TBC1D1-encoding nucleic acid molecule or said complement, said alteration being a cytidine to thymidine transition at the 373rd nucleotide of the TCB1D1 coding sequence of SEQ ID NO:1;

wherein the presence of said alteration identifies a subject at risk for developing obesity.

Claims 2-3 (canceled)

Claim 4 (currently amended): The method of Claim [[3]] 1 wherein said ~~detection~~ assaying step is conducted on genomic DNA.

Claim 5 (currently amended): The method of Claim [[3]] 1 wherein said ~~detection~~ assaying step is conducted on mRNA.

Claim 6 (currently amended): The method of Claim [[2]] 1, wherein said ~~nucleotide variant is detected by a method selected from the group consisting of~~ assaying step comprises at least one of the followings:

a) hybridizing a probe specific for said alteration to RNA isolated from said human sample and detecting the presence of a hybridization product, wherein the presence of said product indicates the presence of said alteration in the sample;

b) hybridizing a probe specific for said alteration to cDNA made from RNA isolated from said sample and detecting the presence of a hybridization product, wherein the presence of said product indicates the presence of said alteration in the sample;

c) hybridizing a probe specific for said alteration to genomic DNA isolated from said sample and detecting the presence of a hybridization product, wherein the presence of said product indicates the presence of said alteration in the sample;

d) amplifying all or part of said TBC1D1-encoding nucleic acid molecule, or complement thereof, in said sample using a set of primers to produce amplified nucleic acids and sequencing the amplified nucleic acids;

e) amplifying part of said TBC1D1-encoding nucleic acid molecule, or complement thereof, in said sample using a primer specific for said alteration and detecting the presence of an amplified product, wherein the presence of said product indicates the presence of said alteration in the sample;

f) molecularly cloning all or part of said TBC1D1-encoding nucleic acid molecule, or complement thereof, in said sample to produce a cloned nucleic acid and sequencing the cloned nucleic acid;

g) amplifying said TBC1D1-encoding nucleic acid molecule, or complement thereof, to produce amplified nucleic acids, hybridizing the amplified nucleic acids to a DNA probe specific for said alteration and detecting the presence of a hybridization product, wherein the presence of said product indicates the presence of said alteration;

h) forming single-stranded DNA from a gene fragment of said TBC1D1-encoding nucleic acid molecule, or complement thereof, from said human sample and single-stranded DNA from a corresponding fragment of a wild-type gene, electrophoresing said single-stranded DNAs on a non-denaturing polyacrylamide gel and comparing the mobility of said single-stranded DNAs on said gel to determine if said single-stranded DNA from said sample is shifted relative to wild-type and sequencing said single-stranded DNA having a shift in mobility;

i) forming a heteroduplex consisting of a first strand of nucleic acid selected from the group consisting of a genomic DNA fragment isolated from said sample, an RNA fragment isolated from said sample and a cDNA fragment made from mRNA from said sample and a second strand of a nucleic acid consisting of a corresponding human wild-type gene fragment, analyzing for the presence of a mismatch in said heteroduplex, and sequencing said first strand of nucleic acid having a mismatch;

j) forming single-stranded DNA from said TBC1D1-encoding nucleic acid molecule, or complement thereof, of said human sample and from a corresponding fragment of an allele specific for said alteration, electrophoresing said single-stranded DNAs on a non-denaturing polyacrylamide gel and comparing the mobility of said single-stranded DNAs on said gel to determine if said single-stranded DNA from said sample is shifted relative to said allele, wherein no shift in electrophoretic mobility of the single-stranded DNA relative to the allele indicates the presence of said alteration in said sample; and

k) forming a heteroduplex consisting of a first strand of nucleic acid selected from the group consisting of a genomic DNA fragment of said TBC1D1-encoding nucleic acid molecule, or complement thereof, isolated from said sample, an RNA fragment isolated from said sample and a cDNA fragment made from mRNA from said sample and a second strand of a nucleic acid consisting of a corresponding gene allele fragment specific for said alteration and analyzing for the presence of a mismatch in said heteroduplex, wherein no mismatch indicates the presence of said alteration.

Claim 7 (withdrawn): The method of Claim 1 wherein said detection step comprises detecting the presence or absence of an amino acid substitution in said TBC1D1 protein.

Claim 8 (withdrawn): The method of claim 7 wherein said alteration is an amino acid substitution selected from the group consisting of R125W, V228G or L392V in a TBC1D1 protein.

Claim 9 (withdrawn): The method of Claim 8 wherein said amino acid substitution is detected by a method selected from the group consisting of:

(a) immunoblotting;

(b) immunocytochemistry;

(c) enzyme-linked immunosorbant or immunofiltration assay; or

(c) assaying the affinity of binding between said TBC1D1 protein and phosophotyrosine, or a peptide containing a phosphotyrosine residue.

Claim 10 (canceled).

Claim 11 (currently amended): The method of claim [[2]] 1, wherein said ~~detection~~ assaying step comprises hybridizing a nucleic acid probe specifically hybridizable to an altered TBC1D1 coding sequence, or complement thereof.

Claim 12 (withdrawn): The method of claim 1 comprising the steps of:

(a) contacting an antibody capable of binding a polypeptide comprising an altered TBC1D1 amino acid sequence but incapable of binding an analogous wild-type TBC1D1 polypeptide; and

(b) detecting binding of said antibody to said altered TBC1D1 polypeptide or lack of binding to said wild-type TBC1D1 polypeptide.

Claim 13 (currently amended): A method for predicting, in a human subject, the likelihood of developing obesity associated with genetic variants of the human *TBC1D1* gene comprising detecting the presence or absence of:

~~a cytidine to thymidine transition at the 466th nucleotide in the sense strand of the first TCB1D1 coding exon, [[(]]SEQ ID NO:33), or the complement thereof;~~

a cytidine to thymidine transition at the 373rd nucleotide of the ~~TCB1D1~~ TBC1D1 coding sequence of SEQ ID NO:1, ~~or the complement thereof;~~

~~a cytidine to thymidine transition at the 373rd nucleotide of the TCB1D1 coding sequence of an alternative transcript comprising the coding sequence encoded by the first TCB1D1 coding exon (SEQ ID NO:33), or the complement thereof;~~

~~or a nucleotide variant that results in an arginine to tryptophan substitution at the 125th amino acid residue of a TBC1D1 protein, or the complement thereof;~~

in a TBC1D1 encoding nucleic acid of said subject;

wherein the presence of said nucleotide variant predicts that said subject has an increased likelihood of developing obesity.

Claim 14 (original): The method of claim 13, wherein said nucleotide variant associated with obesity is detected by determining the genomic sequence of said *TBC1D1* gene.

Claim 15 (withdrawn): A method of screening for drug candidates useful in treating obesity comprising:

(a) preparing an assay solution comprising TBC1D1, or a homolog, derivative, or fragment thereof,

(b) measuring the level of biological activity of said TBC1D1, or a homolog, derivative, or fragment thereof in the presence and absence of a test compound, and

(c) detecting a difference in said biological activity in the presence or absence of said test compound;

wherein a detected difference in said biological activity in the presence and absence of said test compound indicates that said test compound is a drug candidate.

Claim 16 (withdrawn): The method of Claim 15, wherein said biological activity is the binding of phosphotyrosine, or a phosphotyrosine-containing peptide, by TBC1D1.

Claim 17 (withdrawn): The method of Claim 15, wherein said biological activity is the ability to form protein:protein interactions.

Claim 18 (withdrawn): The method of Claim 15, wherein said TBC1D1, or the homolog, derivative, or fragment thereof, is an altered form thereof, bearing an amino acid substitution.

Claim 19 (withdrawn): The method of Claim 18, wherein said altered form bears an amino acid substitution, relative to SEQ ID NO:2, selected from the group consisting of R125W, V228G or L392V.

Claim 20 (withdrawn): The method of claim 15 further comprising testing said drug candidate in cell or animal obesity disease model.